

**Letter of Amendment #2 for:**  
**IMPAACT 2010**  
**Phase III Study of the Virologic Efficacy and Safety of**  
**Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy**  
**Regimens in HIV-1-Infected Pregnant Women and their Infants**

**Version 2.0, dated 8 December 2017**

**DAIDS Study ID #30129**  
**IND #133,438**

**Letter of Amendment Date: 23 August 2019**

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**Information/Instructions to Study Sites from the Division of AIDS**

The information contained in this Letter of Amendment (LoA) affects the IMPAACT 2010 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All applicable IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. Because this LoA does not impact the IMPAACT 2010 informed consent forms, re-consenting of previously enrolled participants is not required, unless sites are instructed otherwise by their IRBs/ECs or other regulatory entities.

Upon obtaining IRB/EC approvals and any other applicable regulatory entity approvals, sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT 2010. If the IMPAACT 2010 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

**IMPAACT 2010**  
**Phase III Study of the Virologic Efficacy and Safety of**  
**Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy**  
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**Version 2.0, Letter of Amendment #2**  
**Letter of Amendment Signature Page**

I will conduct this study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Investigator of Record  
(printed)

## Summary of Modifications and Rationale

The purpose of this LoA is to:

- Permit use of plasma stored at the Screening Visit for maternal HIV-1 RNA (viral load) testing. Such testing may be of interest to further characterize the virologic profiles of mothers enrolled in the study and to assist with interpretation of study outcomes for mothers who may have had a suppressed viral load at study entry. No additional blood will be collected for this testing. Testing will be performed at the same central laboratory designated to perform HIV-1 RNA testing for the secondary study objective evaluating virologic suppression to less than 50 copies/mL at delivery.
- Clarify that statistical analyses of maternal creatinine levels and creatinine clearance rates will be based on severity grades determined from the absolute values of these outcome measures. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, referenced in protocol Section 7.3.3, provides severity grading for these parameters based on both absolute value and change from baseline. Because mothers are pregnant at study entry, and experience physiologic changes during pregnancy that affect these parameters, changes in these parameters from baseline do not provide a valid measure of renal function over time (antepartum and postpartum). Therefore, analyses of these outcome measures will be based on absolute values.
- Clarify that statistical analyses of infant bone outcome measures will be based on absolute bone mineral content (BMC) values. Because international normative BMC values have not been established for infants, Z-scores will not be used for these analyses.
- Add a secondary study objective and associated outcome measures and statistical analyses related to the effects of study drug regimens on changes in maternal weight. Results of recent studies have suggested that regimens containing dolutegravir (DTG) may be associated with weight gain, as may regimens containing tenofovir alafenamide (TAF) (1, 2). The applicability of these results to pregnant and postpartum women is unclear; therefore, data on maternal weight collected in this study will be analyzed for these possible effects.

### References:

1. Bourgi K, Rebeiro PF, Turner M, Castilho JL, Hulgán T, Raffanti SP, et al. Greater Weight Gain in Treatment Naive Persons Starting Dolutegravir-Based Antiretroviral Therapy. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. 2019.
  2. Gomez M, Seybold U, Roider J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017. *Infection*. 2019;47(1):95-102.
- Add as a new appendix to the protocol (Appendix VI) the listing of prohibited and precautionary medications that was previously posted on the study-specific website. The posted listing is dated 5 October 2018 and its content remains current as of the date of this LoA. The listing is being added as an appendix to the protocol at the request of DAIDS.
  - Update links to websites where DAIDS resources for key aspects of study implementation can be accessed.

## Implementation

Modifications of protocol text are provided below, generally in order of appearance in the protocol. Where applicable, modified text is shown using strikethrough for deletions and bold type for additions.

1. Section 2.2, secondary objective 2.2.7, added:

### **2.2.7 Whether changes in maternal weight differ for any pairwise comparison or when comparing a DTG-containing regimen to EFV/FTC/TDF**

This addition is also incorporated into the protocol Schema (edits not shown).

2. Section 5.9, second sentence:

A list of prohibited medications ~~will be~~ **is included in Appendix VI and** posted on the study-specific website: <http://impaactnetwork.org/studies/IMPAACT2010.asp>.

3. Section 5.10:

A list of medications that should be used with caution while on study drug ~~will be~~ **is included in Appendix VI and** posted on the study-specific website: <http://impaactnetwork.org/studies/IMPAACT2010.asp>.

4. Section 6.1, within the procedural table for Screening Visits, row for Laboratory, Blood, last bullet point:

- Stored plasma for antiretroviral resistance testing **and possible HIV-1 RNA testing**

5. Section 7.3.1, first paragraph:

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual), which is available **at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>** ~~on the DAIDS RSC website at: <http://rsc.techres.com/safetyandpharmacovigilance>~~.

6. Section 7.3.1, second paragraph, last sentence:

This form is available **at <https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>** ~~on the DAIDS RSC website at: <http://rsc.techres.com/safetyandpharmacovigilance>~~.

7. Section 7.3.3, first paragraph, second sentence:

This table is available **at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>** ~~on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safetyreporting/daids-grading-tables>~~.

8. Section 9.2, table rows for 9.2.1.2 and 9.2.2.4, second bullet point in each row:
  - Maternal grade 3 or higher adverse events, including events resulting in death due to any cause, through 50 weeks postpartum (refer to Section 7.3.3 for severity grading; **for this outcome measure, grade 3 or higher creatinine levels and creatinine clearance rates will be defined based on absolute values (>1.8 x ULN for creatinine, <60 mL/min for creatinine clearance rate))**)
9. Section 9.2, table row for 9.2.2.7, added, corresponding to secondary objective 2.2.7:
  - **Change in maternal weight antepartum (from study entry to delivery)**
  - **Change in maternal weight postpartum (from delivery to 50 weeks postpartum)**
  - **Change in maternal weight overall (from study entry to 50 weeks postpartum)**
10. Section 9.2, table row for Other Outcome Measures, third bullet point:
  - Infant whole body and lumbar spine BMC **values Z-scores** based on DXA scan at 26 weeks postpartum
11. Section 9.6, last paragraph, added:
 

**The results of any HIV-1 RNA testing performed with plasma stored at the Screening Visit will be analyzed descriptively. For statistical analyses that evaluate virologic change from baseline, the HIV-1 RNA result from the study Entry Visit will be considered the baseline value.**
12. Section 9.6.2, last paragraph, added:
 

**Longitudinal maternal pregnancy weight, postpartum weight, and weight since randomization will be compared by arm with a time and arm interaction using generalized estimating equations. Analyses will compare each arm to the other arms (all pairwise comparisons) and compare the EFV-containing arm to the DTG-containing arms.**
13. Section 13.2, fourth paragraph:
 

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which is available at <https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations> on the RSC website at ~~<http://rsc.tech-res.com/clinicalresearch-sites/protocol-registration>~~.
14. Added Appendix VI, Prohibited and Precautionary Medications, as shown starting on the next page.

## Appendix VI

### Prohibited and Precautionary Medications

The following information may not be all-inclusive. Our understanding of drug interactions continues to grow as new information becomes available. Please refer to the most up-to-date prescribing information (package inserts) and the following drug interaction websites when determining the significance of potential drug interactions; these websites are regularly updated as new information becomes available:

- HIV drug interaction: [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- inPractice: <http://www.inPractice.com>

Any mother enrolled in IMPAACT 2010 who requires a prohibited medication must have the relevant study drug(s) held or permanently discontinued. Upon identification of the need for a prohibited medication, the site investigator should consult the IMPAACT 2010 Clinical Management Committee (CMC) for further guidance on study drug management. Consultation with the CMC is recommended but not required for precautionary medications.

Per protocol Section 5.8.1, mothers who have not initiated cotrimoxazole or isoniazid prophylaxis prior to study entry should preferably defer initiation of these medications until at least two weeks after initiation of their study drug regimen, if eligible to initiate such prophylaxis per local standards of care.

Refer to protocol Section 8.4 for additional information on management of mothers who require rifampin-containing treatment for active tuberculosis (TB).

The remainder of this document provides further information on medications considered prohibited or precautionary with concurrent use of each study drug agent.

*Note:* With respect to IMPAACT 2010 exclusion criterion 4.2.4 (eighth bullet point), receipt of any antiretrovirals (ARVs) within the 14 days prior to study entry — as allowed per inclusion criterion 4.1.3 and exclusion criterion 4.2.4 (seventh bullet) — should not be considered exclusionary when assessing eligibility for this study. Upon enrollment, mothers will discontinue any non-study-supplied ARVs and begin taking study-supplied ARVs consistent with their random assignment (i.e., ARVs that might otherwise be noted as prohibited in this document will not be co-administered with study-supplied ARVs).

## 1 Precautionary and Prohibited Medications for Dolutegravir (DTG)

### 1.1 Prohibited Medications for DTG

DTG should NOT be coadministered with dofetilide.

DTG is metabolized by UGT1A1 with some contribution from CYP3A. DTG is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp *in vitro*. Drugs that induce these enzymes and transporters may decrease DTG plasma concentration and reduce the therapeutic effect of DTG. Coadministration of DTG and drugs that inhibit these enzymes may increase DTG plasma concentration.

The following drugs should NOT be coadministered with DTG, either due to established or potential significant interactions or due to lack of data to guide DTG dosing:

- Nevirapine
- Oxcarbazepine
- Phenytoin
- Phenobarbital
- St. John's wort

## 1.2 Precautionary Medications for DTG

The following drugs should be used with caution:

- Cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications (DTG should be taken two hours before or six hours after taking these medications; alternatively, DTG and supplements containing calcium or iron can be taken together with food)
- Etravirine (coadministration *without* atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended)
- Efavirenz, fosamprenavir/ritonavir, and tipranavir/ritonavir (dose of DTG should be adjusted per the package insert)
- Carbamazepine (dose of DTG should be adjusted per the package insert)
- Rifampin (refer to protocol Section 8.4; the CMC should be informed of all TB diagnoses and consulted on study drug management, with the general expectation the dose of DTG will be adjusted per the package insert during the period of rifampin treatment)
- Metformin (dose of metformin should be limited or adjusted per the package insert)

## 2 Precautionary and Prohibited Medications for Tenofovir Alafenamide (TAF)

### 2.1 Prohibited Medications for TAF

TAF should not be coadministered with tenofovir disoproxil fumarate (TDF) or other drugs containing TDF (e.g., EFV/FTC/TDF, FTC/FPV/TDF, EVG/COBI/FTC/TDF, or FTC/TDF). TAF also should not be coadministered with other TAF-containing products (e.g., FTC/FPV/TAF).

*Note:* Receipt of TAF or TDF within the 14 days prior to study entry should not be considered exclusionary.

TAF is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp activity may lead to changes in TAF absorption. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect and development of resistance.

Due to interactions that decrease TAF concentrations, the following drugs should NOT be coadministered with TAF:

- Tipranavir/ritonavir

- Rifabutin, rifampin, and rifapentine (refer to protocol Section 8.4; the CMC should be informed of all TB diagnoses and consulted on study drug management, with the general expectation that TAF will be replaced with TDF during the period of TB treatment with these drugs)
- St. John's wort

## 2.2 Precautionary Medications for TAF

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of TAF with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Because of this, the following drugs, if administered systemically (and not only topically), should be used with caution:

- Acyclovir, cidofovir, ganciclovir, valacyclovir, and valganciclovir
- Aminoglycosides (e.g., gentamicin)
- High-dose or multiple NSAIDs

The following drugs should also be used with caution:

- Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin (an alternative anticonvulsant should be considered)

## 3 Precautionary and Prohibited Medications for Tenofovir Disoproxil Fumarate (TDF)

### 3.1 Prohibited Medications for TDF

TDF should NOT be coadministered with adefovir dipivoxil.

TDF should not be coadministered with tenofovir alafenamide (TAF) or other drugs containing TAF (e.g., FTC/RPV/TAF). TDF also should not be coadministered with other TDF-containing products (e.g., EFV/FTC/TDF, FTC/RPV/TDF, EVG/COBI/FTC/TDF, or FTC/TDF).

*Note:* Receipt of TDF or TAF within the 14 days prior to study entry should not be considered exclusionary.

TDF also should NOT be coadministered with atazanavir without ritonavir.

### 3.2 Precautionary Medications for TDF

Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of TAF with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Because of this, the following drugs, if administered systemically (and not only topically), should be used with caution:

- Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir
- Aminoglycosides (e.g., gentamicin)
- High-dose or multiple NSAIDs



The following drugs should also be used with caution:

- Didanosine (coadministration increases didanosine concentrations; use with caution and monitor for didanosine-associated adverse reactions, including pancreatitis and neuropathy; dose of didanosine may be adjusted per the package insert)
- Lopinavir/ritonavir, atazanavir coadministered with ritonavir, and darunavir coadministered with ritonavir (coadministration increases tenofovir concentrations; use with caution and monitor for TDF-associated adverse reactions)
- Ledipasvir/sofosbuvir (coadministration increases tenofovir concentrations; use without a protease inhibitor with caution and monitor for TDF-associated adverse reactions; when a protease inhibitor is used, consider an alternative Hepatitis C or antiretroviral therapy)

## **4 Precautionary and Prohibited Medications for Emtricitabine (FTC)**

### **4.1 Prohibited Medications for FTC**

FTC should not be coadministered with lamivudine (3TC) or other drugs containing 3TC. FTC also should not be coadministered with other emtricitabine-containing products (e.g., EFV/FTC/TDF, FTC/RPV/TDF, EVG/COBI/FTC/TDF, or FTC/TDF).

*Note:* Receipt of FTC within the 14 days prior to study entry should not be considered exclusionary.

### **4.2 Precautionary Medications for FTC**

Because FTC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of FTC with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC and other renally eliminated drugs and this may increase the risk of adverse reactions. Because of this, the following drugs, if administered systemically (and not only topically), should be used with caution:

- Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir
- Aminoglycosides (e.g., gentamicin)
- High-dose or multiple NSAIDs

## **5 Prohibited and Precautionary Medications with Efavirenz (EFV)**

### **5.1 Prohibited Medications for EFV**

EFV should NOT be coadministered with other NNRTIs.

*Note:* Receipt of EFV within the 14 days prior to study entry should not be considered exclusionary.

The following drugs should NOT be coadministered with EFV because of potential loss of therapeutic effect or because data are not available on drug-drug interactions:

- Unboosted fosamprenavir calcium
- Indinavir and saquinavir
- Boceprevir and simeprevir
- Carbamazepine (alternative anticonvulsant treatment should be used)
- Itraconazole, ketoconazole, and voriconazole (alternative antifungal treatment should be used)

There is limited information available on the potential for a pharmacodynamics interaction between EFV and drugs that prolong the QTc interval. QTc prolongation has been observed with the use of EFV. Alternatives to EFV should be considered when coadministered with a drug with a known risk of Torsade de Pointes. Use of atovaquone/proguanil is not recommended with EFV.

## 5.2 Precautionary Medications for EFV

EFV has been shown in vivo to induce CYP3A and CYP2B6. Other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when coadministered with EFV. Drugs that induce CYP3A activity (e.g., phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of EFV resulting in lowered plasma concentrations.

The following drugs should be used with caution:

- Fosamprenavir/ritonavir, atazanavir, and lopinavir/ritonavir (refer to package inserts for dose adjustments for these drugs)
- Ritonavir (monitor for elevation of liver enzymes and for adverse clinical experiences)
- Maraviroc (refer to package insert for this drug)
- Warfarin (monitor INR and adjust warfarin dose if necessary)
- Phenytoin and phenobarbital (monitor for anticonvulsant plasma levels)
- Bupropion and sertraline (adjust dose of these drugs based on clinical response)
- Posaconazole (avoid use unless benefit outweighs risk)
- Rifabutin and rifampin (refer to protocol Section 8.4 and the package insert for EFV; the CMC should be informed of all TB diagnoses and consulted on study drug management during the period of rifampin treatment)
- Artemether/lumefantrine and macrolide antibiotics, including clarithromycin (alternative treatment should be considered as should the risk:benefit ratio of adding drugs that may have a risk of QTc prolongation)
- Diltiazem and other calcium channel blockers, e.g., felodipine, nicardipine, nifedipine, verapamil (refer to package inserts for dose adjustments for these drugs)
- HMG-CoA reductase inhibitors, including atorvastatin, pravastatin, and simvastatin (refer to package inserts for dose adjustments for these drugs)
- Hormonal contraceptives, including oral ethinyl estradiol/norgestimate and implant etonogestral (reliable barrier methods of contraception should be used in addition to hormonal contraceptives)
- Immunosuppressants, including cyclosporine, tacrolimus, sirolimus, and others metabolized by CYP3A (refer to package inserts for dose adjustments for these drugs)
- Methadone (monitor for signs of methadone withdrawal and increase dose if required to alleviate withdrawal symptoms)